

REMARKS

Applicants have amended paragraph [0124] of the specification to include the following language:

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. Although development work has been done on the preparation of capsules from methylcellulose and calcium alginate, gelatin, because of its unique properties, remains the primary composition material for the manufacture of capsules. The hard gelatin capsule, also referred to as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely surrounding the drug formulation. The soft elastic capsule (SEC) is a soft, globular, gelatin shell somewhat thicker than that of hard gelatin capsules.

This language is taken from Rudnic *et al.*, Chapter 89 of *Remington's Pharmaceutical Sciences*, 18th Ed., pages 1658 and 1662, copies of which were previously submitted as Exhibit 1.

Applicants have added the above text, which was incorporated by reference in ¶[0176], to make explicit that Applicants contemplate customary capsules having a shell (typically made of gelatin) enclosing a single compartment containing the pharmaceutical formulation of active compound(s) and carriers and/or excipients. In addition, as ¶[0124] makes clear, Applicants also contemplate multicompartment hard capsules with control release properties and water permeable capsules with a multi-stage drug delivery system:

Further, multicompartment hard capsules with control release properties as described by Digenis *et al.*, U.S. Pat. No. 5,672,359, and water permeable capsules with a multi-stage drug delivery system as described by Amidon *et al.*, U.S. Pat. No. 5,674,530 may also be used to formulate the compositions of the present invention. *Specification* at ¶[0124] (emphasis added).

Applicants maintain that no new matter was added in the amendment of ¶[0124], as Applicants are permitted to add the actual text of material incorporated by reference:

The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter. *M.P.E.P. §2163.07(b)* (emphasis added).

Applicants have also amended paragraph [0174] of the specification to correct an obvious error. Figure 3 shows that most of the oligonucleotide is released quickly from granules

comprising 25% bioadhesive, and that in contrast, less oligonucleotide is released from the granules comprising 50% bioadhesive in the earlier fractions. This is consistent with the data in Figure 2, and ¶[0172], which states that “the largest amount of bioadhesive (50%) released the least amount of oligonucleotide at 3, 6, 10 and 15 minutes.” Applicants submit that the correction of the obvious error in ¶[0174] does not constitute the addition of new matter. See *M.P.E.P.* §2163.07 II (“An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction.”).

Applicants have amended claims 30 and 40 to recite a carrier particle-forming substance, and preparation of first and second populations of carrier particles which are combined in a pharmaceutical formulation. Support for these amendments can be found, for example, at ¶¶[0017], and [0033]-[0035]. Claims 35, 38-39, and 41-42 are amended to clarify the claims. Claims 43 and 50 are amended to recite that the preparation of the unit dosage form comprises preparing a first population of carrier particles by combining drug particles comprising drug and carrier particle-forming substance with bioadhesive material, and preparing a second population of carrier particles. Support for these amendments can be found, for example, at ¶¶[0017] and [0164]-[0172]. Support for new claim 56 can be found, for example, at ¶¶[0015]-[0017], and [0164]-[0172]. For the reasons discussed below, Applicants respectfully traverse the rejections of the pending Office Action.

Objection to Amendment of the Specification

The Examiner has objected to the previously submitted amendment to the specification which is again presented herein under 35 U.S.C. § 132(a) “because it introduces new matter into the disclosure.” *Office Action* at 2. The Examiner states that “[i]t is acknowledged that Applicants have incorporated by reference the source for the new text,” but that the insertion of the text into the specification “is improper because the amendment must be accompanied by an affidavit or declaration by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application.” *Office Action* at 2 (citing *In re Hawkins*, 486 F.2d 569 (C.C.P.A. 1973)). Applicants respectfully traverse the objection.

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In the previously submitted amendment, Applicants stated that the material being added was previously incorporated by reference, and that no new matter was added:

This language is taken from Rudnic et al., Chapter 89 of Remington's Pharmaceutical Sciences, 18th Ed., pages 1658 and 1662, copies of which are attached hereto as Exhibit 1 for the Examiner's convenience. Applicants have added the above text, which was incorporated by reference in ¶[0176], ... Applicants maintain that no new matter was added in the amendment of ¶[0124], as Applicants are permitted to add the actual text of material incorporated by reference.... Amendment and Response filed May 25, 2007 at 6 (emphasis added).

Applicants submit that this statement is sufficient to satisfy rule 37 C.F.R. § 1.57(f), which states:

(f) Any insertion of material incorporated by reference into the specification or drawings of an application must be by way of an amendment to the specification or drawings. Such an amendment must be accompanied by a statement that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 C.F.R. § 1.57(f) (emphasis added).

There is no requirement in the rule that the statement be in the form of an affidavit or declaration. In addition, M.P.E.P. § 608.01(p) states that “[a] statement that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter is also required,” – there is no requirement for an affidavit or declaration. The quotation of a previous version of the M.P.E.P. by the court in *In re Hawkins* does not change the requirements under the currently pending rules and M.P.E.P.

To make compliance with rule 37 C.F.R. § 1.57(f) and M.P.E.P. § 608.01(p) explicit, Applicants' representative hereby states for the record that the material added by amendment is the same as the material incorporated by reference, as an examination of previously submitted Exhibit 1 demonstrates, and further states that no new matter is added.

Applicants respectfully request that the amendment to the specification be entered.

35 U.S.C. § 112, First Paragraph, Written Description and Enablement

The Examiner has rejected claims 48 and 54 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, asserting that the addition of the term “single compartment capsule” constitutes new matter. The Examiner asserts the amendment to

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paragraph [0124] was not entered, and that the instant paragraph [0124] “does not contemplate using the species which is a single compartment capsule.” *Office Action* at 4. Applicants respectfully traverse.

Paragraph [0124] makes clear that Applicants contemplated the use of single compartment capsules. Applicants disclose the use of capsules, and state that “[**further**, multicompartment hard capsules...” are also contemplated. As used in paragraph [0124], “further” clearly means in addition. If it is contemplated that “multicompartment hard capsules” can be used in addition to something else, the obvious question is: “In addition to what?” The answer that would be obvious to anyone of skill in the art is that multicompartment capsules are contemplated in addition to single-compartment capsules. The Examiner must explain why one of skill in the art would not recognize this basic idea.

To make explicit that that Applicants contemplated customary capsules having a shell (typically made of gelatin) enclosing a single compartment containing the pharmaceutical formulation of active compound(s) and carriers and/or excipients, Applicants have amended paragraph [0124] of the specification to include the following language:

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft, soluble container or shell of a suitable form of gelatin. Although development work has been done on the preparation of capsules from methylcellulose and calcium alginate, gelatin, because of its unique properties, remains the primary composition material for the manufacture of capsules. The hard gelatin capsule, also referred to as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely surrounding the drug formulation. The soft elastic capsule (SEC) is a soft, globular, gelatin shell somewhat thicker than that of hard gelatin capsules.

This amendment to the specification is proper for the reasons discussed above. When combined with the statement in paragraph [0124] that multicompartment capsules were further contemplated, it would be more than clear to one of skill in the art that at the time of filing Applicants were in possession of the invention as claimed in pending claims 48 and 54.

Applicants note that the Examiner has indicated that entry of the amendment to paragraph [0124] of the specification would obviate the instant rejection. *Office Action* at 8. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 48 and 54 over the recitation of the phrase “single compartment capsule.”

The Examiner has also rejected the claims as lacking enablement, stating that “since a disclosure cannot teach one to make or use something that has not been described.” *Office Action* at 4-5. For at least the above reasons, Applicants submit that the pending claims are adequately described, and therefore request that the Examiner withdraw the enablement rejection of claims 48 and 54 as well.

35 U.S.C. §§ 102(b) and 103(a) – Anticipation and Obviousness

The Examiner has rejected claims 30-36, and 38-55 under 35 U.S.C. § 102(b) as anticipated by McKay, US Patent No. 5,877,309. The Examiner asserts that McKay teaches a method comprising administering to a subject a composition comprising all of the structural elements of the instant claims, and therefore, the method of McKay would necessarily have the same results as the instant claimed method. *Office Action* at 5-6. The Examiner also rejects pending claims 30, 33, and 37 under 35 U.S.C. § 103(a) as obvious over McKay in view of Bennett, which is cited for its disclosure of SEQ ID NO:1. Applicants respectfully traverse.

Applicants reject the Examiner’s assertion that McKay teaches administration of a composition “comprising all of the structural elements of instant claims.” *Office Action* at 5. McKay does not disclose the use of two discrete populations of carrier particles as claimed in the instant application, and therefore does not anticipate or render the pending claims obvious.

As amended, independent claims 30 and 40 recite in part:

wherein said pharmaceutical formulation is prepared by preparing said first population of carrier particles, preparing said second population of carrier particles, and combining said first population of carrier particles with said second population of carrier particles.

Similarly, new claim 56 recites in part:

wherein said pharmaceutical formulation is prepared by preparing said first population of carrier particles by combining said drug and said bioadhesive material, preparing said second population of carrier particles, and combining said first population of carrier particles with said second population of carrier particles.

Pending independent claims 30, 40 and 56 make clear that the claimed methods require the administration of pharmaceutical formulations that comprise separate and distinct populations of carrier particles – the first and second populations of carrier particles are prepared

separately, and then combined. None of the cited references teach preparation or administration of pharmaceutical formulations having at least two distinct populations of carrier particles. Simply combining ingredients in a homogeneous mixture as disclosed in the cited references does not result in the formation of two distinct populations of carrier particles, and does not satisfy the limitations of independent claims 30, 40 and 56 which all require the preparation of two populations of carrier particles prior to bringing the populations together in a single pharmaceutical formulation.

It is believed that the administration of a formulation comprising two distinct populations of carrier particles provides the claimed methods with an advantage that is not found in the cited references. First, by preparing a first population of carrier particles comprising a drug and a bioadhesive, "the drug will acquire some degree of adhesive properties which will extend its residence time and, consequently, absorptive potential, over the region of intestinal mucosa made permeable by penetration enhancers." *Specification* at ¶[0015]. In addition, by having a separate population of carrier particles comprising penetration enhancers, it is believed that a further advantage is gained:

... Upon dissolution in the intestine, the penetration enhancers are released and move down the intestine while acting on the mucosal membrane. Concurrently, the drug-bioadhesive component adheres to the mucosal membrane and releases drug both directly to the penetration enhancer-activated mucosal membrane and into the luminal solution from where it can also be absorbed. In this manner, tissue will be activated prior to the arrival of the drug which will transit through a maximum area of activated tissue, minimizing the possibility of any drug transiting ahead of the penetration enhancer and consequently through unactivated tissue where it could not be absorbed. *Specification* at ¶[0016] (emphasis added).

McKay does not teach preparing a population of carrier particles comprising drug and bioadhesive material that will adhere to the mucosal membrane. Nor does McKay disclose a second population of carrier particles comprising penetration enhancer that activates intestinal tissue prior to the arrival of the drug which has adhered to the mucosal membrane. Simply combining ingredients in a homogeneous mixture does not provide the structural or functional features recited in the pending claims.

The fact that the Examiner is glossing over the distinction between a formulation comprising two separate populations of carrier particles and a formulation comprising a homogeneous mixture of ingredients is apparent from the Examiner's rejection of claims 44 and

55 which recite “wherein said second population of carrier particles further comprises an enteric coating.” The Examiner states that McKay “also teaches that the formulation which comprises the second population of carriers can further comprise an enteric coating...” *Office Action* at 5-6 (emphasis added).

However, the portion of McKay cited by the Examiner does not discuss enteric coatings for a population of carrier particles in a formulation. Instead, McKay discloses that “[e]nteric coatings for acid-resistant tablets, capsules and caplets are known in the art and typically include acetate phthalate, propylene glycol and sorbitan monooleate.” *McKay* at col. 21, lines 1-4. There is no mention in McKay of a pharmaceutical formulation comprising two populations of carrier particles, one of which comprises an enteric coating. McKay discloses enteric coatings for the entire pharmaceutical formulation – tablet, capsule, or caplet. The Examiner tries to overcome this distinction by conflating formulation and carrier particles when the two are not the same.

Because McKay does not teach each and every limitation of independent claims 30, 40 and 56, McKay does not anticipate the pending claims. The deficiencies in McKay identified above are not overcome by combining McKay with Bennett, as neither reference teaches the preparation and use of two distinct populations of carrier particles.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the pending claims under 35 U.S.C. §§ 102(b) and 103(a) as anticipated and obvious over McKay, alone or in combination with Bennett.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history

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shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications of Assignee

Applicants wish to draw the Examiner's attention to the following patent(s) or application(s) of the present application's assignee. Applicants encourage the Examiner to review and monitor the prosecution of the following patent(s) and/or application(s) throughout the pendency of this application.

Patent or Serial Number	Title	Issued/Filed
09/944,493	PULSATILE RELEASE COMPOSITIONS AND METHODS FOR ENHANCED INTESTINAL DRUG ABSORPTION	08/22/2001
11/000,814	PULSATILE RELEASE COMPOSITIONS AND METHODS FOR ENHANCED GASTROINTESTINAL DRUG ABSORPTION	12/01/2004

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CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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